THE PESTICIDE REREGISTRATION PROCESS: COLLECTIONS OF HUMAN HEALTH HAZARDS DATA FOR 3-CHLORO-P-TOLUIDINE HYDROCHLORIDE (DRC-1339)

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ABSTRACT: The 1988 Amendments to the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) accelerated the reregistration schedule for pesticide products registered with the Environmental Protection Agency (EPA) prior to 1984. The compound 3-chloro-p-toluidine hydrochloride (DRC-1339), an avicide registered to control 14 pest bird species, was included on Pesticide List B published by EPA. For the reregistration of DRC-1339, 44 studies were required — 22 product chemistry, 7 wildlife/aquatic hazards, 8 human/domestic animal hazards, 5 environmental fate, and 2 residue chemistry studies. In 5 acute human-health-hazards studies, DRC-1339 was found to: (1) have an oral LD_{50} of 330 (272-401) mg/kg in rats, (2) have a dermal LD_{50} of >2.0 g/kg in rabbits, (3) cause corrosive effects to the eyes of rabbits, (4) cause corrosive effects to the skin of rabbits, and (5) induce dermal sensitization in guinea pigs. Results support the current precautionary statements on the "use labels" warning of harmful ingestion, inhalation, dermal absorption and eye irritation effects to users of the active ingredient.

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INTRODUCTION

The chemical 3-chloro-p-toluidine hydrochloride ($C_7H_9NCl_2$; DRC-1339) is an effective avicide that is used in a pelleted bait marketed under the tradename Starlicide Complete® by Purina Mills, Inc., St. Louis, MO (Besser et al. 1967, Decino et al. 1966, Schafer 1981). Because DRC-1339 is highly toxic (LD_{50}<10 mg/kg) to most passerines, columbids, and corvids but only moderately toxic (LD_{50}>100 mg/kg) to most raptors and mammals, the chemical is considered selective for target species. Risks of primary or secondary hazards to non-target animals are low (Cunningham et al. 1981; Savarie and Schafer 1986, Schafer 1984).

The reregistration of DRC-1339 is a priority of the U. S. Department of Agriculture (USDA), Animal and Plant Health Inspection Service (APHIS), Animal Damage Control (ADC) Program (Knittle et al. 1990). Purina Mills, Inc. and APHIS currently have 2 Federal (FIFRA Section 3) and 28 State (FIFRA Section 24C) registrations for the compound. These cover 6 general applications, including pigeons on/near urban structures or rural non-crop areas, gulls on/near coastal islands, blackbirds foraging on grain at livestock feedlots, blackbirds at large roost-staging areas, corvids depredating on newborn calves/lambs, and corvids foraging on endangered/threatened species. Altogether, 14 target species are cited on the "use labels"; these include: pigeon (*Columba livia*), herring gull (*Larus argentatus*), great black-backed gull (*Larus marinus*), ring-billed gull (*Larus delawarensis*), common raven (*Corvus corax*), common crow (*Corvus brachynchos*), Brewer's blackbird (*Euphagus cyanocephalus*), brownheaded cowbird (*Molothrus ater*), common grackle (*Quisculus quiscula*), great-tailed grackle (*Cassidix mexicanus*), red-winged blackbird (*Agelaius phoeniceus*), starling (*Sturnus vulgaris*), tricolored blackbird (*Agelaius tricolor*), and blackbilled magpie (*Pica pica*).

This paper presents: (1) an overview of the FIFRA-1988 Process which directed the 9-year, 5-phase reregistration schedule for pesticide products, (2) a description of the Code of Federal Regulations (CFR) 40 (Parts 150-189) which established basic procedures for the conduct of pesticide tests (EPA 1991), and (3) a summary of 5 acute human-health-hazards studies submitted to the EPA in support of DRC-1339 reregistration.

THE FIFRA-1988 PROCESS

DRC-1339 was originally registered in 1967 (Knittle et al. 1990). Only minimal environmental safety and human health hazards data were required at that time. The 1972 amendments to FIFRA, titled the Federal Environmental Control Pesticide Act, mandated that all pesticides must meet registration data requirements (be reregistered) within a 5-year period (Fagerstone et al. 1990). EPA was directed to reevaluate the environmental safety/human hazards associated with about 600 active ingredients and 45,000 formulated products. Because of the magnitude of this task, progress by EPA was slow. In 1988, Congress amended FIFRA to accelerate EPA's reregistration efforts. FIFRA-1988 required that all pesticides containing an active ingredient first registered prior to November 1, 1984 must be reregistered within a 9-year period in 5 phases.

Phase 1

In Phase 1 EPA issued 4 lists (A, B, C, D) of active ingredients (A.I.) subject to reregistration. List A contained 194 groups of related pesticide active ingredients (350 specific A.I.) for which EPA had issued Registration Standards before the effective date of FIFRA-1988. Remaining pesticides were divided into 3 lists (Lists B—229 A.I., C—288 A.I., and D—286 A.I.) based upon their potential for human exposure and environmental risks. DRC-1339 appeared on List B dated May 25, 1989.

Phase 2

This phase gave registrants 90 days to notify EPA whether or not they intended to reregister their active ingredients, to commit to providing necessary new studies, and to pay newly imposed reregistration and maintenance fees (Fagerstone 1990). Because the low-volume use of DRC-1339 technical product (<100 lbs./year) made it economically

infeasible for Purina Mills, Inc. (the technical registrant) to maintain the technical product registration, USDA/APHIS formed an informal consortium with Purina to reregister DRC-1339. Purina and USDA/APHIS mutually projected a continued need for the compound as an agricultural avicide and agreed to provide 22 product chemistry, 7 wildlife/aquatic hazards, 8 human/domestic animal hazards, 5 environmental fate, and 2 residue studies required to reregister the DRC-1339 A.I.

Phase 3

Phase 3 required registrants to provide summaries of existing studies that might be used to support reregistration, to initiate new studies, and to identify known adverse effects. For DRC-1339, no summaries of prior studies were submitted, but 44 new studies were initiated in Phase 2. To date, 39 of these studies have been completed and submitted to EPA.

Phase 4

During this Phase, EPA reviewed the data submitted. A Data Call-In was received from EPA on February 25, 1991 identifying 13 additional studies of which 6 were ultimately required (3 Product Chemistry, 1 Human/Domestic Animal Hazards, and 2 Environmental Fate studies). These are included in the total studies cited under Phase 3.

Phase 5

In Phase 5 EPA will review all the submitted studies and decide whether or not to reregister the active ingredient — issue/not issue a "Registration Eligibility Document (RED)." The EPA will also identify specific studies that will be needed for reregistration of end-use products (the field formulations).

DATA REQUIREMENTS

40 CFR (Parts 150-189) specifies the types of chemical/ environmental/ human health hazards studies required for pesticide registration or reregistration (EPA 1991). It also defines technical terms and outlines Good Laboratory Practice (GLP) standards to be used in data collections. Twelve "Subdivisions" to the Code specify the types of data to be provided by the registrant(s) for an active ingredient (see Figure 1). Each of these Subdivisions contains a matrix of the studies required for the chemical's "general use pattern" (terrestrial: food/non-food crop; aquatic: food/non-food crop; greenhouse: food/non-food crop; forestry; domestic outdoor; and indoor) and "test substance" (manufacturing-use product or end-use product).

The specific studies that compose Subdivision F (Hazards Evaluation: Human and Domestic Animals) are included under 5 categories: Acute, Subchronic, Chronic, Mutagenicity, and Special Testing. In this paper, we present a summary of 5 recently completed Acute Tests for DRC-1339: (1) Acute Oral Toxicity—Rat (GRN 81-1), (2) Acute Dermal Toxicity—Rabbit (GRN 81-2), (3) Primary Eye Irritation—Rabbit (GRN 81-4), (4) Primary Dermal Irritation—Rabbit (GRN 81-5), and (5) Dermal Sensitization—Guinea Pig (GRN 81-6) (see Fig. 1).

ACUTE HUMAN-HEALTH-HAZARDS STUDIES FOR DRC-1339

Based on negotiations between EPA, Purina Mills, Inc., and USDA/APHIS, the following 5 acute, human health hazards studies were required for reregistration of DRC-1339. These studies were contracted to MB Research Laboratories, Inc., Spinnerstown, PA. All studies adhered to Good Laboratory Practice provisions as specified in 40 CFR Part 160. Data from these studies could impact the wording of precautionary statements to human users of DRC-1339 included on the pesticide "use labels."

40 CFR DATA CATEGORIES

Subdivision	Title
D	Product Chemistry
E	Hazard Evaluation: Wildlife and Aquatic Organisms
F	Hazard Evaluation: Humans and Domestic Animals
G	Product Performance
I	Experimental Use Permits
J	Hazard Evaluation: Nontarget Plants
K	Reentry Protection
L	Hazard Evaluation: Nontarget Insect
M	Biorational Pesticides
N	Environmental Fate
O	Residue Chemistry
R	Spray Drift Evaluation

DRC-1339 ACUTE STUDY REQUIREMENTS UNDER PHASES 2 AND 3 OF FIFRA-1988 (Subdivision F)

GRN No.	Title
81-1	Acute Oral Toxicity (LD_{50} Rat)
81-2	Acute Dermal Toxicity (LD_{50} Rabbit)
81-4	Primary Eye Irritation (Rabbit)
81-5	Primary Dermal Irritation (Rabbit)
81-6	Dermal Sensitization (Guinea Pig)

Figure 1.The 12 Subdivisions of tests presented in 40 CFR that may be required to register/reregister a pesticide (top); and, the acute data required for reregistration of DRC-1339 (Subdivision F–Hazard Evaluation: Humans and Domestic Animals) under Phases 2 and 3 of FIFRA-1988 (see EPA 1991).

Acute Oral Toxicity—Rat
(Single Oral Dose LD_{50}) (GRN 81-1)

Objective—This test was conducted to determine the acute toxicity of DRC-1339 when administered via gavage as a single oral dose to male and female albino rats (*Rattus norvegicus*).

Methods—Following a quarantine period of at least 1 week, 5 healthy male and 5 female Wistar albino rats (each approximately 8 weeks old and weighing between 200-300 g) were randomly assigned to each of 5 dose groups (247, 312, 500, and 1000 mg/kg); an additional group of 5 female rats was tested at 277 mg/kg to further clarify the dose re-

sponse function for that gender. The pre-test weight range was 204-300 g for males and 212-253 g for females. The weight variation of the animals did not exceed ±20% of the mean weight. Rats were identified by cage notation and indelible body marks, and were housed 1/cage in suspended wire mesh cages. Bedding was placed beneath the cages and changed twice/week. Fresh Purina Rat Chow Diet #5012[1] (Purina Mills, Inc., St. Louis, MO) was provided *ad libitum*, except for 16-20 h prior to dosing (fasted). Water was available *ad libitum*.

The animal room (reserved exclusively for rats on acute tests) was temperature controlled (19-21° C), with a 12:12 h light:dark (0600-1800 and 1800-0600 h) schedule. The test substance (97.1% DRC-1339) was used as a 25% w/v dilution in distilled water for each dose level.

Each rat received the respective oral dose via gavage. The rats were observed 1, 2, and 4 h post dose, and once daily thereafter for 14 successive days to determine toxicity and pharmacological effects. Each animal was observed twice daily for mortality. Body weights were recorded immediately pretest, weekly, and at death or study termination (survivors). All animals were necropsied for gross pathology.

Results—Mortality (male:female) to the 5 doses was: 247 mg/kg (1:1), 277 (no males tested:1), 312 mg/kg (0:5), 500 mg/kg (4:5), and 1000 mg/kg (5:5). Deaths occurred by Day 6 and were preceded by physical signs of lethargy, ataxia (uncoordinated movements), muscle flaccidity, negative righting reflex, chromodacryorrhea (reddish ocular discharge), ptosis (partial eyelid closure with constricted pupil), piloerection, tachypnea (increased respiration rate), chromorhinorrhea (colored discharge from nose), coma, prostration, brown staining of bodily areas, and wetness of the nose/mouth area. Necropsy of the dead rats revealed abnormalities of the lungs, liver, kidneys, urinary bladder, heart, and gastrointestinal tract, as well as wetness and brown staining of the nose/mouth and anogenital areas.

Physical signs noted in survivors included: lethargy, ataxia, piloerection, muscle flaccidity, tachypnea, chromorhinorrhea, and wetness or brown staining of the nose/mouth area. Body weight effects were minimal, however, instances of weight loss or less than normal weight gain were noted for several rats. The LD_{50} values (95% confidence intervals) were: males — 350 (267-458) mg/kg, females — 303 (263-349) mg/kg, and males/females combined — 330 (272-401) mg/kg of body weight (Litchfield and Wilcoxon 1949).

According to EPA toxicology criteria, DRC-1339 is a Category II Toxicant (LD_{50} >50 but <500 mg/kg).

Acute Dermal Toxicity (LD_{50})—Rabbit (GRN 81-2)

Objective—This test was conducted to determine the potential toxicity of DRC-1339 when applied dermally and kept in contact with the skin of rabbits for 24 h.

Methods—Following a quarantine period of at least 1 week, 5 healthy male and 5 healthy female New Zealand albino rabbits (*Oryctolagus cuniculus*) were randomly selected for test. The minimum and maximum pretest weights of the rabbits were 2.3 to 2.4 kg (males) and 2.1 to 2.5 kg (females). Animals were identified by cage notation and uniquely numbered metal ear tags; they were housed 1/cage in suspended wire mesh cages. The rabbits were provided fresh Purina Rabbit Chow Diet #5321 (Purina Mills, Inc., St. Louis, MO) and water *ad libitum*. The animal room (reserved exclusively for rabbits on acute tests) was temperature controlled (19-21° C); a 12:12 h light:dark schedule (0600-1800 and 1800-0600 h) was used. Approximately 24 h before application of the test substance (97.1% DRC-1339), a large (10% of body surface) dorsal spot on the back of each rabbit was shaved; the skin of each animal was checked and found to be intact (unbroken) prior to test.

The DRC-1339 was moistened (made pasty) with distilled water, and applied onto the shaved dermal site, 1 time, via syringe-type applicator. The dose was 2.0 g/kg of body weight based upon the weight of the dry DRC-1339. The site was then covered with a gauze patch, secured with non-irritating tape (gentle pressure was applied to the gauze to distribute the product over the covered site). The torso was then wrapped with thin plastic to prevent rubbing/scratching of the treated area and secured with non-irritating tape. At 24 h, the patch was removed, and the residual DRC-1339 was washed off the skin with water. Test sites for each rabbit were scored for dermal irritation at 24 h post dose and on Days 7 and 14 using the Draize Dermal Scale (Draize 1944). Additional toxic signs were also described.

Regarding general toxicity and pharmacological signs, the rabbits were observed at 1, 2, and 4 h post dose and once daily throughout the 14-day test. Each rabbit was observed twice daily for mortality during this period. Body weights were recorded pretest, weekly, and at termination of the test. All rabbits were necropsied and examined for gross pathology upon completion of Day 14.

Results—All rabbits survived the 2.0 g/kg dermal application. Physical signs of diarrhea, few feces, and soiling of the anogenital area were noted in some animals.

No rabbits showed changes in body weights. Dermal reactions, slight to well-defined on Day 1, were absent to severe by Day 14 (considerable variability observed). The treated skin of all rabbits was stained orange at 24 h. Slight to well-defined erythema (redness) was observed for 6 of 10 rabbits at 24 h, with 3 males eventually scored as severe by Day 7; whereas, 2 males continued to be scored as having severe erythema at Day 14. Edema (fluid production/drainage) was observed on all rabbits at 24 h, but then decreased to slight edema on 4 rabbits at Day 7; no animals showed edema on Day 14. Additional signs that were evident for at least a portion of the rabbits were most frequent on Day 7 and included: orange skin, flaking skin, and shiny areas. Necropsies revealed abnormalities of the treated skin, liver, kidneys, intestines, and urinary bladder; data for 1 rabbit (male) appeared "normal."

The LD_{50} was determined to be >2.0 g/kg of body weight —no deaths recorded. Thus, DRC-1339 is classed as a Category III Toxicant for dermal effects—>2000 mg/kg.

Primary Eye Irritation—Rabbit (GRN 81-4)

Objective—The objective was to determine the irritation/corrosive effects of DRC-1339 when instilled into the eyes of rabbits. This is a derivation of the well-known "Draize Test" (Draize et al. 1944).

Methods—Following quarantine of at least 1 week, 6 healthy New Zealand albino rabbits (free from ocular irritation) were designated for test. Minimum and maximum pre-

[1]Reference to trade names does not imply endorsement by the U.S. Government.

test body weights of the rabbits were 2.3 and 2.5 kg, respectively. The rabbits were identified by cage notation and a uniquely numbered metal ear tag. Rabbits were housed 1/cage in suspended wire mesh cages located within a temperature-controlled (19-21° C) animal room that was reserved exclusively for rabbits on acute tests with a 12:12 h (0600-1800 and 1800-0600 h) light:dark schedule in effect. Fresh Purina Rabbit Chow Diet #5321 (Purina Mills, Inc., St. Louis, MO) and water were provided *ad libitum*.

Approximately a 0.1 ml equivalent (mean of 54 mg) of dry DRC-1339 (97.1%) was placed into the conjunctival sac of 1 eye of each rabbit; the contralateral eye served as a control. After instillation, the eyelids were held together for approximately 1 sec; the eyes were not washed. Ocular responses were graded according to the Draize Scale (i.e., maximum scores of 80, 10 and 20 were possible for cornea, iris, and conjunctivae, respectively); these were recorded at 1 h post instillation and on Days 1, 2, 3, and 7 of a scheduled 21-day test (Draize 1944). The eyes of each rabbit were examined using sodium fluorescein for the Day-1 grading of corneal effects; sodium fluorescein penetrates corneal disturbances and shows the area of ocular effect during the early observations. Reversible change to the eye was considered evidence of irritation; irreversible tissue damage to the anterior surface of the eye was considered evidence of corrosion.

Results—Corneal opacity, iritis, and severe conjunctival irritation were noted in the test eyes of all 6 rabbits, and these symptoms persisted through Day 7. Due to the severity of the corneal, iris, and conjunctival reactions (corrosive effects) in all of the rabbits, the study was terminated on Day 8 of the test for "humaneness reasons." An expert veterinary ophthalmologist inspected the animals and prepared a detailed report to justify early termination. Diarrhea was the only abnormal systemic sign noted during the observation period.

The test substance (DRC-1339) is considered to be a Category I Toxicant—corrosive (irreversible destruction of ocular tissues) or corneal involvement or irritation persisting for more than 21 days.

Primary Dermal Irritation—Rabbits (GRN 81-5)

Objective—This test was conducted to determine the irritant or corrosive effects of DRC-1339 when applied dermally and kept in contact with the skin of rabbits for 4 h.

Methods—Following at least 1 week of quarantine, 6 healthy New Zealand albino rabbits (approximately 8 weeks old) were selected for this test. Pretest body weights of the rabbits were between 2.1 and 2.4 kg. The rabbits were identified by cage notation and uniquely numbered metal ear tags. Animals were housed 1/cage in suspended wire mesh cages located in a room reserved exclusively for rabbits on acute tests. This room was temperature-controlled (19-21° C), with a 12:12 h light:dark (0600-1800 and 1800-0600 h) schedule. Body weights of each rabbit were recorded pretest.

Approximately 24 h prior to the application of DRC-1339, about a 10 cm^2 area on the dorsal trunk of each animal was shaved; the site remained intact (unbroken) for all animals. On Day 1, 0.5 g of DRC-1339 (moistened with distilled water to form a paste) was placed on the treated site of each animal for 4 h. A gauze patch was place over the paste and secured with non-irritating adhesive tape; the torso of the rabbit was then wrapped with a semi-occlusive dressing and secured with adhesive tape to retard evaporation of volatile substances. At the end of 4 h, the wrappings and gauze were removed, and the site was washed gently with water to remove residual DRC-1339.

Rabbits were observed for skin reactions at 30 and 60 min after removal of the site coverings and at 24, 48, and 72 h post removal. Erythema and edema were scored according to the Draize Dermal Technique (Draize et. al. 1944). Dermal irritation was defined as the production of reversible inflammatory changes to the skin; dermal corrosion referred to irreversible tissue damage to the skin. Ulceration, necrosis, and possible tissue destruction were also observed. To determine reversibility of DRC-1339 produced skin effects, measurements were made on Days 7 and 14.

Results—Dermal scores were variable for the 6 rabbits. Erythema scores ranged from slight to moderate at 1 and 24 h post patch removal and slight to severe at 48 and 72 h post removal. Erythema remained slight to severe on Days 7 and 14. Edema was slight to moderate at 1 h post patch removal but absent to well-defined throughout the remainder of the test. Instances of moderate eschar (black areas and areas of shiny skin indicative of injuries in depth) were noted during the test. Instances of diarrhea for certain rabbits were the only abnormal systemic signs noted.

Based on the observed "injuries in depth" (eschar) to some rabbits, DRC-1339 is judged to be a Category I Toxicant for dermal effects following 4 h of contact — corrosive (tissue destruction into the dermis or scarring for some animals).

Dermal Sensitization — Guinea Pig (GRN 81-6)

Objective—The objective of this test was to determine the potential of DRC-1339 to promote skin sensitization reactions after repeated topical "skin insult" applications in guinea pigs.

Methods—Following quarantine of at least 5 days, 34 healthy male Hartley albino guinea pigs (*Cavia cobaya*) were selected for the test. Pretest body weights of the animals were between 355 and 400 g. Each guinea pig was identified by specific cage notation and a uniquely numbered ear tag. The animals were housed 1/cage in suspended rodent-type cages. Fresh Purina Guinea Pig Chow Diet #5025 (Purina Mills, Inc., St. Louis, MO) and water were available *ad libitum*. The animals were maintained in a temperature-controlled (19-21° C), light-/dark-controlled (0600-1800 and 1800-0600 h) room that was reserved exclusively for guinea pigs on acute tests.

The test procedure used the Buehler Method. Prior to initiation of the study, a topical preliminary screen was conducted using 4 guinea pigs. This was to determine a "mildly irritating" and a "highest non-irritating" concentration of DRC-1339. A dorsal area of about 5 by 10 cm on each animal was clipped free of hair 24 h prior to test (skin unbroken). Eight concentrations of DRC-1339 (0.1, 0.5, 1, 5, 10, 25, 50, and 100%) were prepared using distilled water; the 100% concentration was prepared by mixing the dry chemical with a few drops of distilled water. Each animal received 4 concentrations of DRC-1339 (i.e., 1 at each of 4 sites/guinea pig). Except for the 100% concentration, which was applied as a paste and covered with a gauze patch, the concentrations were placed onto the skin and covered with a 25-mm Hilltop Chamber (a clear plastic cover). Finally, the sites were covered with a rubber dental dam large enough to span the 4

sites. Two pieces of elastoplast tape were used to cover the dam. The DRC-1339 remained in place for 6 h. Then, the tape, dam, chambers, and gauze were removed; residual DRC-1339 was washed away with distilled water and the sites dried using soft toweling. The treated sites were examined and scored at 24 and 48 h post application using the Draize Dermal Scoring Technique (Draize et al. 1944). Based on irritation scores, the "mildly irritating concentration" chosen for the sensitization study was the 100% dose and the "highest non-irritating concentration" was the 25% dose.

The main sensitization study involved 30 guinea pigs assigned to 4 groups; these animals were housed, treated, and prepared essentially the same as those in the preliminary screen. The total study involved a 38-day sequence consisting of a 21-day induction phase, a 14-day waiting phase, and a 3-day challenge phase. Group 1 (n=10) received 3 topical inductions over a 3 week period of the "mildly irritating" (100%) concentration. Group 2 (n=5) served as the non-induced control for DRC-1339; this Group would be tested during the challenge phase only. Group 3 (n=10) served as a "positive control"; this group was dosed with a 0.2% concentration of Dinitrochlorobenzene (DNCB) in the same manner as the DRC-1339 animals—DNCB is a known dermal senitizer. Finally, Group 4 (n=5) served as the non-induced control for DNCB; this Group received applications of DNCB only during the challenge phase. Skin reactions of guinea pigs in Groups 1 and 3 were recorded at 24 and 48 h after induction.

Two weeks after the third induction with DRC-1339 or DNCB, Groups 1 and 2 were challenged with a 25% concentration of DRC-1339, and Groups 3 and 4 were challenged with a 0.1% concentration of DNCB. Skin reactions of the guinea pigs in each of the 4 groups were scored at 24, 48, and 72 h post challenge application.

Results—Erythema of the dermal sites was absent to mild following Induction 1, mild to severe following Induction 2, and absent to mild following Induction 3. Edema was absent to mild following Induction 1, slight to mild following Induction 2, and absent to barely perceptible following Induction 3.

During the challenge phase, positive responses were noted in 7 of 10 DRC-1339-treated guinea pigs and 6 of 10 DNCB controls. Erythema ranged from barely perceptible to mild at 24 h, absent to slight at 48 h, and absent to very slight at 72 h for DRC-1339 animals. Edema, absent at 24 h, was absent to slight in select animals by 48 h post challenge, and absent to very slight at 72 h post challenge. There were no positive responses to the challenge concentrations (25% DRC-1339 or 0.1% DNCB) in the non-induced control guinea pigs.

Due to the frequencies and severities of reactions during the challenge phase, both DRC-1339 and DNCB are considered "dermal sensitizers."

CONCLUSIONS

Reregistration of DRC-1339 is progressing on schedule; the 44 studies required to address potential adverse environmental/human-health effects will be completed in 1994. Results from the 5 acute studies conducted to provide data for Subdivision F (40 CFR Part 158.34) Requirements showed that DRC-1339: (1) has an oral LD_{50} of 330 (272-401) mg/kg in rats, (2) has a dermal LD_{50} of >2.0 g/kg in rabbits, (3) causes corrosive effects to the eyes of rabbits, (4) causes corrosive effects to the skin of rabbits, and (5) induces dermal sensitization in guinea pigs. The "precautionary statements" for DRC-1339 contained in the upper left portion of pesticide "use labels" currently read:

> Harmful if swallowed, inhaled, or absorbed through the skin. Avoid contact with eyes, skin, or clothing. Handle only with protective gloves, clothing, and face mask, or respirator. Wash hands with soap and water after handling.

These precautions concur with the previously described results.

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